Message

From: Harvey Clewell [HClewell@ramboll.com]
Sent: 6/6/2019 7:59:27 PM
To: Bahadori, Tina [Bahadori.Tina@epa.gov]
Subject: RE: chloroprene -- in vitro system

Thanks

With kind regards
Harvey Clewell
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From: Bahadori, Tina [mailto:Bahadori.Tina@epa.gov]
Sent: Thursday, June 6, 2019 3:54 PM
To: Harvey Clewell <HClewell@ramboll.com>
Subject: RE: chloroprene -- in vitro system

Certainly.

From: Harvey Clewell <HClewell@ramboll.com>
Sent: Thursday, June 6, 2019 3:53 PM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>
Subject: RE: chloroprene -- in vitro system

Ok, I guess this will be a good thing to talk about at the meeting next Wednesday.

With kind regards
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From: Bahadori, Tina [mailto:Bahadori.Tina@epa.gov]
Sent: Thursday, June 6, 2019 3:45 PM
To: Harvey Clewell <HClewell@ramboll.com>; Thayer, Kris <thayer.kris@epa.gov>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; mandersen [Ex. 6 Personal Privacy (PP)]; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Sonja Sax <SSax@ramboll.com>; Ken Mundt <kenneth.mundt@cardno.com>; Miyoung Yoon [Ex. 6 Personal Privacy (PP)]; Kenyon, Elaina <Kenyon.Elaina@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: chloroprene -- in vitro system

No, nothing changed. This has always been the case.
Tina

From: Harvey Clewell <HClewell@ramboll.com>
Sent: Thursday, June 6, 2019 3:34 PM
To: Thayer, Kris <thayer.kris@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; mandersen[Ex. 6 Personal Privacy (PP)]Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Sonja Sax <SSax@ramboll.com>; Ken Mundt <kenneth.mundt@cardno.com>; Miyoung Yoo[Ex. 6 Personal Privacy (PP)]; Kenyon, Elaina <Kenyon.Elaina@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: chloroprene -- in vitro system

Interesting…that's certainly not what I remember from the meeting. I remember agreeing to work with Paul to come to rough agreement on the PBPK model so that it would not be necessary for NCEA to ask for a separate peer review of the model itself. Maybe that changed?

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From: Thayer, Kris [mailto:thayer.kris@epa.gov]
Sent: Thursday, June 6, 2019 3:23 PM
To: Harvey Clewell <HClewell@ramboll.com>; Bahadori, Tina <Bahadori.Tina@epa.gov>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; mandersen[Ex. 6 Personal Privacy (PP)]; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Sonja Sax <SSax@ramboll.com>; Ken Mundt <kenneth.mundt@cardno.com>; Miyoung Yoon[Ex. 6 Personal Privacy (PP)]Kenyon, Elaina <Kenyon.Elaina@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: chloroprene -- in vitro system

Harvey,

See if this helps. These are the action items from our July 19, 2018 meeting
https://cfpub.epa.gov/ncea/iris2/event_attachment.cfm?layout=none&attach_id=544

Available at https://cfpub.epa.gov/ncea/iris2/events.cfm#stakeholderMeetings

Kris

From: Harvey Clewell <HClewell@ramboll.com>
Sent: Thursday, June 6, 2019 3:16 PM
To: Thayer, Kris <thayer.kris@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; mandersen[Ex. 6 Personal Privacy (PP)]Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Sonja Sax <SSax@ramboll.com>; Ken Mundt <kenneth.mundt@cardno.com>; Miyoung Yoon[Ex. 6 Personal Privacy (PP)]; Kenyon, Elaina <Kenyon.Elaina@epa.gov>;

Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: chloroprene -- in vitro system

Hi Chris, Tina

I'm confused. Last year when the CAAT reviewed the IRIS assessment for ETBE and tBA and we just reviewed the PBPK model as part of the overall IRIS peer review. Is there a reason you would want to do it separately this time?

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From: Thayer, Kris [mailto:thayer.kris@epa.gov]
Sent: Thursday, June 6, 2019 6:24 AM
To: Bahadori, Tina <Bahadori.Tina@epa.gov>; Harvey Clewell <HClewell@ramboll.com>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; mandersen Ex. 6 Personal Privacy (PP) ; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Sonja Sax <SSax@ramboll.com>; Ken Mundt <kenneth.mundt@cardno.com>; Miyoung Yoon Ex. 6 Personal Privacy (PP) ; Kenyon, Elaina <Kenyon.Elaina@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: RE: chloroprene -- in vitro system

And, as a reminder, last year we discussed the option to address any hard to resolve scientific differences of opinion on the model via the peer review charge questions.

From: Bahadori, Tina
Sent: Thursday, June 6, 2019 6:16 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; mandersen Ex. 6 Personal Privacy (PP) ; Thayer, Kris <thayer.kris@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Sonja Sax <SSax@ramboll.com>; Ken Mundt <kenneth.mundt@cardno.com>; Miyoung Yoon Ex. 6 Personal Privacy (PP) ; Kenyon, Elaina <Kenyon.Elaina@epa.gov>; Schlosser, Paul <Schlosser.Paul@epa.gov>
Subject: QRE: chloroprene -- in vitro system

Harvey, thanks for this feedback. I will let Paul and his team continue the conversation about the requisite experiment(s) and model QA/QC. But I want to emphasize -- and this will matter when we meet next week – the focus of this engagement is on the **model** and its acceptability in the context of this Request for Reconsideration. We are not having a discussion about the risk calculations. In fact, if we agree to proceed, what will go to peer review will be the report on the model itself (without the discussion of risk calculations). I would like to stay focused so that we can have an appropriate review of and closure on the model. Should the model complete peer review, we will then apply to the IRIS assessment and take that updated assessment for peer review as well. At the meeting next week we will go over the next steps.

Thanks,

Tina

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Tina Bahadori, Sc.D.
Director, National Center for Environmental Assessment (EPA/ORD/NCEA)
National Program Director, Human Health Risk Assessment (EPA/ORD/HHRA)

From: Harvey Clewell <HClewell@ramboll.com>
Sent: Wednesday, June 5, 2019 6:34 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; mandersen [Ex. 6 Personal Privacy (PP)]; Thayer, Kris <thayer.kris@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Sonja Sax <SSax@ramboll.com>; Ken Mundt <kenneth.mundt@cardno.com>; Miyoung Yoon [Ex. 6 Personal Privacy (PP)] Kenyon, Elaina <Kenyon.Elaina@epa.gov>
Subject: RE: chloroprene -- in vitro system

Hi Paul

I would love to be able to get back to doing research to investigate your hypothesis regarding diffusion limitation in the liquid phase. However, even though the experiment you describe may sound simple, performing it correctly would be just as difficult as the original studies conducted by Matt Himmelstein. Unfortunately, there is no longer anyone conducting these kinds of studies. Both John Wambaugh at NCCT and I have tried to identify laboratories with experience in conducting in vitro metabolism studies with volatiles, but we have both been unsuccessful. That is why Denka had to use an environmental contract laboratory to conduct the Kg study.

I have discussed this question with Miyoung Yoon, who is now at FDA, and it was she who suggested that the presence of microsomes in Matt's studies would have greatly increased the availability of chloroprene for metabolism by competing with other sources of non-specific binding. She is the most experienced researcher in the area of *in vitro* metabolism that I know of. I'm afraid this difference in opinion will need to go unresolved, however, not only because the necessary studies are impractical but also because the relevance of any new results to Matt's published studies would be highly uncertain. The difficulty is that Kg is just an empirical parameter that represents the rate of mass transfer under specific experimental conditions. Most importantly, as mixing is increased, the transition from simple diffusion to laminar convection and then to turbulent convection impacts the rate of mass transfer in a nonlinear manner, so extrapolation from one experiment to another would be extremely difficult.

I have also discussed this question with Mel Andersen, and he believes that the published *in vitro* data are completely reliable. He agrees with the approach you suggested for estimating Kg from the male mouse liver metabolism data by fixing Km at the value of 1 uM supported by the literature on cyp2E1 substrates. Re-estimating the metabolism parameters with the estimated Kg results in a 25% decrease in risk compared to using the published values. Values of Kg lower than the value estimated from the metabolism data would reduce risk estimates even further. I just don't see the benefit of performing any additional studies.

With kind regards
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From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Wednesday, June 5, 2019 9:57 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; mandersen Ex. 6 Personal Privacy (PP) ; Thayer, Kris <thayer.kris@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Sonja Sax <SSax@ramboll.com>; Ken Mundt <kenneth.mundt@cardno.com>; Miyoung Yoon Ex. 6 Personal Privacy (PP) ; Kenyon, Elaina <Kenyon.Elaina@epa.gov>
Subject: RE: chloroprene -- in vitro system

I've changed the subject to better reflect the topic.

This morning I realized there's actually a fairly simple experiment that could determine if my hypothesis on diffusion limitation in the liquid phase is correct: run incubations with ½ (or less) of the total incubation mixture, concentrations of microsomes, etc, otherwise the same. (We'd want to have parallel experiments, same lab, same microsomes, etc., with full volume.)

If the system is well mixed, as the current model suggests, then the rate at which chloroprene is removed from the headspace (mass/time) would be reduced by ½, since there's ½ the microsomes doing the work. You'd have to incorporate the change in head-space volume in the calculation (either way).

Alternately, if there is diffusion limitation, with the microsomes near the surface doing the bulk of the metabolism, then the rate of chloroprene removal would not be reduced by ½. A higher fraction of the microsomes would be near the air:liquid interface, so the rate of removal per mg microsome in the system would be higher.

Since the concentration in the incubation solution is effectively calculated by mass balance, this would also lead to an increase in the estimated concentration associated with a given rate of metabolism, I'm pretty sure. The result would then also be an increase in the apparent Km.

Doing these experiments would then evaluate the extent to which mass transport in the liquid phase is limiting in this system, using live/active microsomes, doesn't require any more elaborate analytic methods than already employed.

-Paul

From: Schlosser, Paul
Sent: Tuesday, June 04, 2019 5:14 PM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; mandersen Ex. 6 Personal Privacy (PP) >; Thayer, Kris <thayer.kris@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Sonja Sax <SSax@ramboll.com>; Ken Mundt <kenneth.mundt@cardno.com>; Miyoung Yoon

<yoon.m.work@gmail.com>
Subject: RE: chloroprene -- Bayesian analysis

Harvey, all,

In the Kg experiments, if the sampling of the liquid phase is well into the liquid, away from the air:liquid interface, but mixing is sufficient to keep microsomes evenly distributed, then it's possible for the CP concentration near the surface to be higher, less limited by mass transfer resistance, than in the middle or bottom. If the microsomes near the surface are responsible for the majority of the metabolism, then that could explain the discrepancy between the Kg data/model and the metabolic data.

But that would also mean that the activity of those microsomes was higher than currently estimated… if only 10% of the microsomes (those near the surface) are responsible for the metabolism, the actual Vmax would be 10x higher per mg microsomes, for example. Since the in vivo PK are flow limited, the fits to those data would be the same, if Vmax (in the liver) is actually 10x higher, those in vivo data don't invalidate this hypothesis.

The incubation results would still be linear with microsome content by this explanation, presuming they are well mixed. Using ½ the total microsomes would put that much less near the surface, resulting in a proportional decrease in removal from the gas phase. It's saying that under conditions of high metabolic activity, the assumption of a well-mixed incubation volume is not valid. I think that's more likely than a small fraction of microsomes significantly affecting transport through the entire volume.

Good evening, until tomorrow!

-Paul

From: Harvey Clewell <HClewell@ramboll.com>
Sent: Tuesday, June 04, 2019 2:12 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; mandersen <andersenme@aol.com>; Thayer, Kris <thayer.kris@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>; Sonja Sax <SSax@ramboll.com>; Ken Mundt <kenneth.mundt@cardno.com>; Miyoung Yoon <yoon.m.work@gmail.com>
Subject: RE: chloroprene -- Bayesian analysis

Hi Paul

I do not agree that the apparent discrepancy between the Kg experiments and the metabolism experiments leads to parameter uncertainty. To break the collinearity between Km and Kg, we have followed your suggestion of fixing Km at a value based on the literature for cyp2e1 substrates (1 uM), and have re-estimated Vmax and Kg in the male mouse liver, which shows the highest rates of metabolism. The resulting value of Kg represents the maximum limitation on transport in the in vitro studies that is consistent with the data. It does not demonstrate, however, that there was any significant transport limitation in those studies.

Personally, I have complete confidence in the metabolism data collected by Matt Himmelstein and in the approach he used for its analysis. I see no evidence to support an assumption of transport limitation in his studies. The constants derived in the published analysis are consistent with a large body of work on *in vivo* estimation of kinetic constants for clearance of well-metabolized vapors (i.e., with relatively low Km values). Moreover, assuming that there was a significant limitation on transport in these studies results in Km values that are implausibly low, which in turn results in lower risk estimate compared to use of the published values.

The discussion below of the role of plasma proteins on metabolism is from James Gillette's 1973 paper in the Annals of the NY Academy of Science. He suggested that binding proteins in the plasma can accelerate metabolism by acting as carriers of a drug to the vicinity of the hepatocytes. I believe that microsomal proteins can play a similar role in the *in vitro* studies: in the presence of mixing, non-specific binding of a lipophilic compound to proteins can serve to overcome the transport limitation associated with penetrating the aqueous media. In other words, since chloroprene is lipophilic, diffusion through the aqueous media in the *in vitro* assay would normally be rate-limiting, but if the media is well-mixed and contains microsomal proteins, then non-specific binding of chloroprene to the microsomes could greatly enhance its availability for metabolism.

Unfortunately, investigating this effect in the *in vitro* system would not be at all straightforward, because the microsomal proteins serve both as the site of metabolism and as a source of non-specific binding that competes with the surface of the vial. In fact, I do not believe it is possible to experimentally determine a Kg that would be appropriate in any microsomal metabolism study, because of the dual role that the microsomes play (metabolism and non-specific binding). Denaturing the microsomal proteins in order to eliminate metabolism would also alter their tertiary binding structure.

it is impossible to predict when the dissociation of the drug-protein complex is rate limiting from the association constants alone. It seems probable, however, that the rate of dissociation of the drug-protein complex seldom becomes rate limiting in the metabolism of drugs.

It seems more probable that diffusion of the free drug from the plasma into hepatocytes may be the rate-limiting step in the metabolism of drugs by highly active enzymes in the liver. When this occurs, the bound form of the drug in plasma remains in equilibrium with its free form as the concentration of unbound drug in plasma declines during the passage of the blood through the hepatic sinusoids. However, it is also possible that drug-binding proteins in the cytoplasm of hepatocytes hasten metabolism by maintaining the concentration gradient across the membranes of the hepatocytes and by increasing the amount of drug available to the enzymes located toward the central parts of the cells. Indeed, Y and Z proteins [18–21] are thought to act as carriers of sulfobromophthalein and other anions. But, whether they actually act as carriers or as tissue stores of the anions depends on a number of factors that include the association constants and the concentrations of the proteins as well as on the maximum rate and the K_m values of the drug-metabolizing enzymes and the relative diffusivities of the unbound drug and drug-protein complexes. Because of the complexities of these interrelationships, it is frequently difficult to determine when binding sites in hepatocytes serve as transport mechanisms or as storage mechanisms.

To determine whether plasma proteins act as transport carriers, it is necessary to calculate the apparent clearance on the basis of the concentration of unbound drug in plasma and to compare these apparent clearance values (rate of elimination/concentration of unbound drug) with hepatic blood flow rate. If the apparent clearance exceeds the hepatic blood flow when the drug is known to be eliminated solely by the liver, it may be concluded that the plasma proteins or other components in blood act as transport carriers. When it is not known whether a drug is eliminated solely by the liver, it would be useful to determine whether the clearance value exceeds the cardiac output, because the true clearance can never exceed the cardiac output.

it is impossible to predict when the dissociation of the drug-protein complex is rate limiting from the association constants alone. It seems probable, however, that the rate of dissociation of the drug-protein complex seldom becomes rate limiting in the metabolism of drugs.

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With kind regards
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From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Friday, May 31, 2019 11:41 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry

<rgentry@ramboll.com>; Thayer, Kris <thayer.kris@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>; Kapraun, Dustin <Kapraun.Dustin@epa.gov>
Subject: RE: chloroprene -- Bayesian analysis

Harvey, all,
(Adding Dustin Kapraun: I'll catch you up later.)

Food for thought for June 12:

Regarding the in vitro analyses, the apparent discrepancy between the "Kg" experiments and the metabolic experiments leads to parameter uncertainty. Kg and the Km values can't be estimated independently from only the metabolic experiments, as you state in the manuscript. But to fully estimate the impact of that uncertainty in subsequent risk estimation, one could potentially use the results of a Bayesian analysis, not just the mean values, but the parameter distributions.

So the first estimation of Kgi and P (from data without microsomes) resulted in a joint distribution of these parameters. Some of those data are consistent with a higher P and Kgi than the mean values – the upper data in Figure B-1. Likewise your review of the literature on Km values effectively provides an informed prior on that parameter. Instead of fixing one or the other of these, formal Bayesian analysis could use those as priors when analyzing the data with active microsomes. I wonder if there are values of Kgi and P consistent with the upper end of the Kg-data (ie, within the uncertainty given those data) that are also consistent with the metabolic data?

I presume the Kg experiments, like the metabolic experiments, involved repeated measures, which needs to be properly accounted for in setting up the likelihood calculation in order to estimate the true uncertainty, full possible range of parameters. The number of independent experiments in Figure B-1 is a lot less than the number of data points, yes? (Since there are clusters of pink points at each time point, it's more than the number of colors used.) The estimated parameter uncertainty estimate would be too low if all the data are treated as independent. Likewise for the metabolic experiments.

If it wasn't done this way (accounting for repeated measures in the likelihood; formal Bayesian sequential parameter estimation), how hard would it be? To unpack this fully, and consider options, we may need to have original data by experimental unit (incubation vial), if it's not already set up that way.

-Paul

From: Schlosser, Paul
Sent: Thursday, May 30, 2019 8:06 AM
To: Harvey Clewell <HClewell@ramboll.com>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>; Thayer, Kris <thayer.kris@epa.gov>; Vandenberg, John <Vandenberg.John@epa.gov>; Bahadori, Tina <Bahadori.Tina@epa.gov>; Morozov, Viktor <Morozov.Viktor@epa.gov>; Davis, Allen <Davis.Allen@epa.gov>; Sasso, Alan <Sasso.Alan@epa.gov>
Subject: RE: chloroprene

Harvey, all,
(Copying EPA folk)

In the manuscript, you suggest that binding to the microsomal protein, which wasn't present in the Kg-measurement experiments, could have altered the partitioning between air and liquid phases, thereby resulting in the changed mass transfer. If true, this could be explained in the model by changing the water:air partition coefficient. Maybe you can test the hypothesis that way ahead of our meeting, so we know if it's a valid explanation or not. The microsomal concentration was 0.5 mg/ml, ~ 0.05%, so I don't know that it could alter partitioning too much, but it would be good to know ahead of the 12th if changing the PC alone to any extent could explain the apparent discrepancy.

-Paul

From: Harvey Clewell <HClewell@ramboll.com>
Sent: Tuesday, May 14, 2019 4:40 PM
To: Schlosser, Paul <Schlosser.Paul@epa.gov>
Cc: Jerry Campbell <JCampbell@ramboll.com>; Michael Dzierlenga <MDZIERLENGA@ramboll.com>; Robinan Gentry <rgentry@ramboll.com>
Subject: chloroprene

Hi Paul

Here is the revised manuscript on the chloroprene PBPK model, plus all of the supplemental materials that can be sent via email. The R model and two additional supplemental files (the IISRP report on the in vivo study and the Teklab report on the Kg study) will be transmitted separately, but I don't think you will really need to look at them at this point.

I'm going to be in Netherlands next week for Alina Efremenko's PhD ceremony, so it would be great if we could get together sometime this week to talk about the new analyses documented in the paper. Would that be possible? Jerry and I are free pretty much any time.

With kind regards
Harvey Clewell
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